The Open Public Health Journal
DOI: 10.2174/0118749445416525250909091121, 2025, 18, e18749445416525
ISSN: 1874-9445
1

RESEARCH ARTICLE **OPEN ACCESS**

Association of Nonavalent Human Papillomavirus Vaccine with Abdominal Pain Symptoms: A Post-Marketing Drug Safety Study

Mario Arturo González-Mariño[1,*]

[1]*Department of Obstetrics and Gynecology, Faculty of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia*

Abstract:

Introduction: Human papillomavirus vaccines protect against the types of this virus that most often cause cervical cancer. These vaccines must be safe for the population's use. It is important to detect any adverse event possibly related to vaccination. Abdominal pain has occasionally been reported following HPV vaccination, but its clinical relevance and causal relationship remain unclear. Therefore, this study aimed to assess the association between the 9-valent HPV vaccine and abdominal pain symptoms using simple epidemiological measures applicable in clinical settings.

Methods: The Vaccine Adverse Event Reporting System database was searched for data on all vaccines and their adverse effects, especially the relationship between the human papillomavirus nonavalent vaccine and abdominal pain symptoms, from January 1, 2016, to November 29, 2024. A 2x2 table was designed, and from this, the proportional reporting rate, odds ratio, and Yates' chi-squared test were calculated.

Results: Among 15,005 reports related to the HPV vaccine, 127 (0.85%) involved abdominal pain. For other vaccines, 9,970 of 1,229,411 reports (0.81%) mentioned abdominal pain. The PRR and OR were both 1.04, and Yates' Chi-squared = 0.204 (p = 0.651), indicating no statistically significant difference.

Discussion: PRR and OR are practical tools for early signal detection of potential adverse effects. In this case, they suggest abdominal pain is not disproportionately associated with HPV vaccination.

Conclusion: No statistically significant association was observed between the 9-valent HPV vaccine and abdominal pain compared to other vaccines, supporting its favorable safety profile based on current VAERS data.

Keywords: Papillomavirus vaccines, Uterine cervical neoplasms, Drug-related side effects and adverse reactions, Abdominal pain, Registries, Vaccines, HPV vaccination.

*Address correspondence to this author at the Department of Obstetrics and Gynecology, Faculty of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia; Email: martgoma99@outlook.es

Cite as: González-Mariño M. Association of Nonavalent Human Papillomavirus Vaccine with Abdominal Pain Symptoms: A Post-Marketing Drug Safety Study. Open Public Health J, 2025; 18: e18749445416525.
http://dx.doi.org/10.2174/0118749445416525250909091121

Received: June 02, 2025
Revised: July 26, 2025
Accepted: July 30, 2025
Published: September 15, 2025

1. INTRODUCTION

The World Health Organization launched, in 2020, a global strategy to eliminate cervical cancer, centered on three key targets: ensuring that 90% of girls are fully vaccinated against HPV by age 15; screening 70% of women by age 35 and again by age 45; and providing appropriate treatment for 90% of women with precancerous lesions, as well as effective management for 90% of those with invasive cervical cancer [1].

The human papillomavirus vaccination (HPV) is currently the cornerstone of long-term cervical cancer control [2]. However, as with any other drug, vaccines

may be associated with the occurrence of adverse reactions, although they must have a higher level of safety than the pharmaceuticals used for treatment because they are usually given to people who are healthy and used in large groups of the population. Before vaccines are licensed, their efficacy has to be shown in clinical trials, and any adverse effects should be detected. However, these studies may lack the statistical power to detect rare but potentially serious adverse effects [3]. As a result, when a new vaccine comes to market, there is some uncertainty about its safety profile, specifically about rare events or those occurring a longer time after vaccination. Their administration may occasionally be linked to adverse effects that cannot be detected until the vaccine is administered within large populations [4].

The Vaccine Adverse Event Reporting System database (VAERS, U.S.A) is a spontaneous reporting system for adverse events following vaccination. It serves as the national early warning system for detecting possible safety problems with U.S.-licensed vaccines. Their data are intended to detect signals indicating adverse events that may require further assessment [5].

A signal refers to information (whether from a single source or multiple sources) that indicates a new and potentially causal relationship, or a novel aspect of an existing relationship, between an intervention and an event or group of related events, which may be either adverse or beneficial. This information is considered sufficiently credible to warrant further verification, regardless of its origin. Signals must be investigated, beginning with validation and, if confirmed, followed by hypothesis testing [3, 6].

The HPV vaccine protects against the types of HPV that most often cause cervical cancer. It is expected that with the nonavalent vaccine (9-valent), the prevention of cervical cancer will increase to up to 90% [7]. As of late 2016, the HPV 9-valent vaccine has been the only available vaccine in the United States [8].

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends the HPV vaccine for routine vaccination at age 11 or 12 years (vaccination can be started at age 9). ACIP also recommends vaccination for everyone through the age of 26 years if not adequately vaccinated when younger [9].

Abdominal pain represents a spectrum of conditions. It is a common presentation in the outpatient setting and is challenging to diagnose [10, 11]. Analyses of VAERS reports from 2006 to 2017 identified abdominal pain as one of the most frequently reported gastrointestinal symptoms following quadrivalent HPV vaccination, with 202 serious reports of abdominal pain [12]. These symptoms have also been reported to VAERS with the 9-valent HPV vaccine. However, the existing literature has not focused on signal detection thresholds for abdominal pain in relation to this vaccine.

The objective of this study is to analyze the relationship between the human papillomavirus nonavalent vaccine and abdominal pain symptoms, with procedures that are easy to apply by the clinician, also in other symptoms or drugs, by using the Proportional Reporting Rate (PRR) to measure the proportion of notifications in VAERS of abdominal pain with the 9-valent HPV vaccine. In the same database, this ratio is compared with notifications of the same symptoms but with the other vaccines. If the PRR vaccine-abdominal pain is significantly high, it may represent a sign [13]. Research question: Is abdominal pain more frequently reported after 9-valent HPV vaccination than after other vaccines?

The study hypothesis is that the PRR for abdominal pain following 9-valent HPV vaccination is significantly elevated compared to other vaccines, potentially indicating a safety signal that warrants further investigation.

2. METHODS

This is a post-marketing descriptive pharmacoepidemiologic study based on spontaneous adverse event reports. The VAERS database was searched for reports submitted from January 1, 2016, to November 29, 2024. Various filters were applied to extract information related to the 9-valent HPV vaccine and its association with abdominal pain and other reported symptoms. Similarly, data for all other vaccines were retrieved using the same symptom classification approach to allow for comparative analysis. The analysis focused on individuals aged 6–17 and 18–29 years, which include the recommended vaccination age groups, according to the age intervals in the database.

To evaluate whether abdominal pain was disproportionately reported following HPV vaccination compared to other vaccines, a 2 × 2 contingency table was constructed. From this, the following measures were calculated:

Proportional Reporting Ratio (PRR): to identify whether abdominal pain occurred at a higher-than-expected frequency among HPV vaccine reports.

Odds Ratio (OR): to estimate the strength of association between the 9-valent HPV vaccine and reports of abdominal pain.

Yates' Chi-Squared Test: to adjust for continuity and minimize overestimation of statistical significance in small samples.

These statistical methods were selected for their established role in signal detection within spontaneous reporting systems such as VAERS.

2.1. Ethical Considerations

This study qualifies as minimal-risk research. It involves secondary analysis of anonymized, publicly available data obtained from VAERS. No individual-level data were evaluated, and therefore, Institutional Review Board approval was not required in accordance with applicable ethical standards.

Nonetheless, the interpretation of passive surveillance data must be approached with caution. VAERS data are subject to limitations, including underreporting, reporting

bias, duplicate entries, and a lack of clinical verification. These findings are intended for signal detection and hypothesis generation only and should not be interpreted as evidence of causality or definitive vaccine risk.

3. RESULTS

A total of 15,005 adverse event reports were associated with the 9-valent HPV vaccine in individuals aged 6 to 29 years from January 1, 2016, to November 29, 2024. Of these, 127 reports (0.85%) involved abdominal pain. In contrast, for all other vaccines, 1,229,411 adverse events were reported, among which 9,970 (0.81%) included abdominal pain. Table **1** summarizes the distribution of abdominal pain and other reported adverse events across vaccine types.

Table 1. Adverse effects reported to the VAERS database from 2016 to November 29, 2024, among individuals aged 6 to 29.

Symptoms	9-valent HPV vaccine	9-valent HPV vaccine	Total
Abdominal pain	142 (a)	9955 (b)	10097
All others AEFIs	14863 (c)	1219456 (d)	1234319
Total	15005	1229411	1244416

AEFI=adverse events following immunization.

To evaluate whether abdominal pain was disproportionately reported following the 9-valent HPV vaccine, a 2 × 2 contingency table was constructed. The results of the disproportionality analysis were as follows:

PRR= (a/a+c)/ (b/b+d) = 0.00845/0.00812= 1.04

odds ratio (OR)= ad/bc = 154867007/148288600= 1.04

Yates' chi-squared test =0.204 (p = 0.651)

The test produced a value of 0.204 with 1 degree of freedom, indicating no statistically significant difference in the reporting of abdominal pain between the 9-valent HPV vaccine and other vaccines.

These findings suggest no evidence of disproportionate reporting of abdominal pain following HPV vaccination compared to other vaccines. The PRR and OR values are both close to 1, indicating a nearly identical frequency of abdominal pain reports between the two groups. Clinically, this suggests that abdominal pain is not more commonly associated with the HPV vaccine than with other routine immunizations.

Table **2** shows the general characteristics by age group of reported cases of abdominal pain in the 9-valent HPV vaccine. The majority of cases were reported in the 6–17-year age group (n = 104; 73.2%), which corresponds to the primary target population for HPV vaccination. A smaller number of cases occurred in older age groups, with a few reports lacking specific age data.

In terms of sex distribution, females accounted for 102 of the 142 cases (71.8%), consistent with higher vaccination rates historically seen among females in HPV immunization programs. Among females, 80 events (78.4%) were classified as non-serious, and 20 (19.6%) as serious but non-fatal. No deaths were reported.

When comparing abdominal pain to other reported adverse events following immunization (AEFIs), abdominal pain represented a very small proportion of total reports: 0.85% for the 9-valent HPV vaccine and 0.81% for all other vaccines. The minimal difference resulted in PRR and OR values of 1.04, with no statistically significant signal identified.

Furthermore, the majority of abdominal pain cases were non-serious and self-limiting, with no deaths and few serious reports. This supports the conclusion that abdominal pain, although occasionally reported, is not uniquely or disproportionately associated with the 9-valent HPV vaccine and does not represent a distinct safety concern based on current data.

Table 2. Reported cases of abdominal pain in the 9-valent HPV vaccine. General characteristics by age group, January 1, 2016, to November 29, 2024.

Age	6-17	18 - 29	30-39	40-49	Unknown	Total
N = 142						
Sex						
Male	38	1	1	0	0	40
Female	66	18	13	2	3	102
Seriousness*						
Female						
Non-serious	51	14	12	2	1	80
Non-serious-death	15	4	1	0	0	20
Serious, death	0	0	0	0	0	0
Male						
Non-serious	30	3	1	1	0	35
Serious, non-death	7	0	0	0	0	7
Serious, death	0	0	0	0	0	0

4. DISCUSSION

The 9-valent HPV vaccine safety profile has been evaluated in several studies and is generally considered favorable. A study found three percent more local adverse reactions were observed in women who received the 9-valent HPV vaccine versus the quadrivalent vaccine: RR = 1.03 (95% CI 1.02 to 1.04). However, no significant differences in systemic serious adverse events were noted [14]. The results of this study are in line with this safety profile, particularly in relation to abdominal pain, which appears to be infrequent and generally non-serious.

All vaccines can have some side effects. Abdominal pain and other gastrointestinal symptoms, such as nausea, vomiting, constipation, diarrhea, and distention, are reported with most vaccines [15].

A retrospective study compared the risk of emergency department visits and hospitalizations during the interval shortly after vaccination with the risk during a later interval of a poorly defined category, which included abdominal pain, allergic reactions, syncope, *etc*., obtaining an OR of 1.36, 95% CI: 1.13-1.64. The timing of all of these outcomes was not significant, except for syncope episodes, which were much more likely to occur on the day of vaccination [16].

A randomized, double-blind study was conducted on girls aged 9 to 15 years to evaluate the safety profile of the quadrivalent (4vHPV) and 9-valent human papillomavirus vaccine. Participants were randomly assigned to two groups, each receiving a three-dose regimen of either vaccine. Adverse effects were common in both groups, with 93.3% of participants in the 9-valent human papillomavirus vaccine group and 90.3% in the 4vHPV group reporting at least one adverse event. In the 9-valent human papillomavirus vaccine group, the most frequently reported systemic adverse effects included: Headache (11.4%), fever (5%), nausea (3%), oropharyngeal and upper abdominal pain (2.7 and 1.7%, respectively) [17]. In this study, data from the VAERS database were analyzed to evaluate the frequency and characteristics of abdominal pain reports associated with the 9-valent human papillomavirus vaccine among individuals aged 6 to 29 years and to compare these with all other vaccines. The findings indicated that the 9-valent human papillomavirus vaccine does not significantly increase the risk of abdominal pain when compared to other vaccines, with a proportional reporting ratio (PRR) of 1.04 and an odds ratio of 1.04. Yates' chi-squared test yielded a value of 0.204 (p= 0.651), indicating no evidence of a significant association.

Data mining methods have been proposed as screening tools for improving the efficiency of adverse event reporting. The PRR is a statistic that is used to generate a signal about the potential hazard of drugs (a value close to or less than one may prevent unnecessary additional evaluation) [18]. A signal can be determined with the methods presented above based on simple mathematical procedures, which can be calculated with a basic calculator. However, the number of PRR signals for singleton reports can result in many false alarms and divert resources from more consequential relationships. The screening proportional reporting ratio, which considers the number of reports for a given vaccine ≥3, PRR ≥2, and Yates-corrected chi-square ≥4, eliminates the overweighting of singleton reports [19].

The results obtained from this study found that the 9-valent HPV vaccine is safe regarding the risk of abdominal pain symptoms. However, its presence could stem from anxiety, vagal reactions, coincidental illness, or inflammatory responses.

This study also contributes to understanding demographic patterns in reported cases. Table **2** shows that the majority of abdominal pain reports were in females aged 6 to 17 years, and most were non-serious. No deaths were reported, which aligns with global post-licensure surveillance data indicating a strong safety profile for the HPV vaccine. However, our analysis also highlights the importance of continued monitoring, particularly in specific subpopulations.

Despite its strengths, our study has several limitations. First, VAERS is a passive surveillance system and is subject to underreporting and reporting biases, especially for non-serious events, which may be underrepresented. Second, VAERS reports are not medically verified, and symptom causality or timing is not always clearly documented. Third, we could not account for confounding factors such as concomitant vaccine administration, preexisting health conditions, or psychosomatic reactions. Additionally, the cross-sectional nature of the data and the lack of unvaccinated controls limit our ability to draw causal inferences. Finally, the proportional reporting ratio (PRR), while useful for signal detection, is a hypothesis-generating tool and not a definitive measure of risk.

CONCLUSION

No statistically significant differences in abdominal pain symptoms, when evaluated using epidemiological methods of alert, were observed with the injection of the 9-valent HPV vaccine in relation to the other vaccines. The data available on VAERS do not recommend further research on this association. However, these findings must be interpreted with caution due to the inherent limitations of passive surveillance data. The VAERS system is subject to underreporting, reporting biases, and lacks clinical verification, which restricts its capacity to establish causality. From a public health and clinical perspective, these findings support the favorable safety profile of the 9-valent HPV vaccine and should reinforce confidence in its continued use within recommended age groups. However, healthcare professionals and policy-makers should remain vigilant and support systems that encourage comprehensive and timely adverse event reporting to ensure early detection of any emerging safety concerns.

AUTHOR'S CONTRIBUTIONS

The author confirms sole responsibility for the following: Study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

LIST OF ABBREVIATIONS

HPV	=	Human papillomavirus
PRR	=	Proportional Reporting Rate
OR	=	Odds Ratio
VAERS	=	Vaccine Adverse Event Reporting System database
ACIP	=	Advisory Committee on Immunization Practices
CDC	=	Centers for Disease Control and Prevention
AEFIs	=	Adverse Events Following Immunization
4vHPV	=	Quadrivalent Human Papillomavirus Vaccine

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The data used in this study are publicly available from the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program co-managed by the CDC and FDA. The VAERS database can be accessed at: https://wonder.cdc.gov/vaers.html

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Global strategy to accelerate the elimination of cervical cancer as a public health problem. 2020. Available from: https://www.who.int/citations/i/item/9789240014107

[2] Wilailak S, Kengsakul M, Kehoe S. Worldwide initiatives to eliminate cervical cancer. International Journal of Gynaecology and Obstetrics 2021 Oct; 155(Suppl 1): 102-6. http://dx.doi.org/10.1002/ijgo.13879

[3] Autran B, Asturias EJ, Evans S, *et al*. Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS. Expert Rev Vaccines 2009; 8(6): 705-16. http://dx.doi.org/10.1586/erv.09.40 PMID: 19485752

[4] Chandler RE. Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events. BMJ 2019; 365: l2268. http://dx.doi.org/10.1136/bmj.l2268 PMID: 31151960

[5] Patricia Wodi A, Marquez P, Mba-Jonas A, Barash F, Nguon K, Moro PL. Spontaneous reports of primary ovarian insufficiency after vaccination: A review of the vaccine adverse event reporting system (VAERS). Vaccine 2023; 41(9): 1616-22. http://dx.doi.org/10.1016/j.vaccine.2022.12.038 PMID: 36732165

[6] Beninger P. Signal Management in Pharmacovigilance: A Review of Activities and Case Studies. Clin Ther 2020; 42(6): 1110-29. http://dx.doi.org/10.1016/j.clinthera.2020.03.018 PMID: 32487428

[7] Saraiya M, Unger ER, Thompson TD, *et al*. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst 2015; 107(6): djv086. http://dx.doi.org/10.1093/jnci/djv086 PMID: 25925419

[8] Dilley S, Miller KM, Huh WK, Huh WK. Human papillomavirus vaccination: Ongoing challenges and future directions. Gynecol Oncol 2020; 156(2): 498-502. http://dx.doi.org/10.1016/j.ygyno.2019.10.018 PMID: 31848025

[9] HPV Vaccination Recommendations. 2025. Available from: https://www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html

[10] Yew KS, George MK, Allred HB. Acute Abdominal Pain in Adults: Evaluation and Diagnosis. Am Fam Physician 2023; 107(6): 585-96. PMID: 37327158

[11] Buel KL, Wilcox J, Mingo PT. Acute Abdominal Pain in Children: Evaluation and Management. Am Fam Physician 2024; 110(6): 621-31. PMID: 39700366

[12] Subeesh V, Neha R, Beulah E, Gouri N, Maheswari E. Postlicensure surveillance of human papillomavirus vaccine using the Vaccine Adverse Event Reporting System, 2006–2017. Perspect Clin Res 2020; 11(1): 24-30. http://dx.doi.org/10.4103/picr.PICR_140_18 PMID: 32154146

[13] Pharmacovigilance signals for the Americas. 2016. Available from: https://www3.paho.org/hq/dmdocuments/2016/senales-farmacovigilancia-10-16.pdf

[14] Arbyn M, Xu L, Simoens C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Libr 2018; 2020(3): CD009069. http://dx.doi.org/10.1002/14651858.CD009069.pub3 PMID: 29740819

[15] Lee S, Lee K, Park J, *et al*. Global burden of vaccine-associated hepatobiliary and gastrointestinal adverse drug reactions, 1967–2023: A comprehensive analysis of the international pharmacovigilance database. J Med Virol 2024; 96(7): e29792. http://dx.doi.org/10.1002/jmv.29792 PMID: 38993028

[16] Hansen J, Yee A, Lewis N, *et al*. Safety of 9-valent human papillomavirus vaccine administered to males and females in routine use. Vaccine 2023; 41(11): 1819-25. http://dx.doi.org/10.1016/j.vaccine.2022.11.009 PMID: 36396513

[17] Vesikari T, Brodszki N, van Damme P, *et al*. A Randomized, Double-Blind, Phase III Study of the Immunogenicity and Safety of a 9-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine (V503) Versus Gardasil® in 9–15-Year-Old Girls. Pediatr Infect Dis J 2015; 34(9): 992-8. http://dx.doi.org/10.1097/INF.0000000000000773 PMID: 26090572

[18] Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001; 10(6): 483-6. http://dx.doi.org/10.1002/pds.677 PMID: 11828828

[19] Banks D, Woo EJ, Burwen DR, Perucci P, Braun MM, Ball R. Comparing data mining methods on the VAERS database. Pharmacoepidemiol Drug Saf 2005; 14(9): 601-9. http://dx.doi.org/10.1002/pds.1107 PMID: 15954077